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ATTACHMENT-RELATED REGULATORY PROCESSES MODERATE THE IMPACT OF ADVERSE CHILDHOOD EXPERIENCES ON STRESS REACTION IN BORDERLINE PERSONALITY DISORDER

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In this study, the authors explored whether attachment insecurity moderates the effects of adverse childhood experiences on stress reactivity in the context of borderline personality disorder (BPD). Participants were 113 women (39 with BPD, 15 with some BPD criteria present, 59 without any BPD symptoms) who participated in the Trier Social Stress Test. Saliva samples were collected before and after the stressor and assayed for salivary alpha-amylase (sAA) and cortisol. Adverse childhood experiences were measured using the Childhood Trauma Questionnaire, and attachment by the Experiences in Close Relationships-Revised questionnaire. Results revealed that attachment avoidance and a combination of more adverse childhood experiences and attachment insecurity resulted in higher sAA levels and differences in reactivity to the stressor. Interactions between

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attachment anxiety and adverse childhood experiences were related to blunted cortisol reactivity. The results suggest that the influence of adverse childhood experiences on stress regulation in BPD may be moderated by attachment-related regulatory processes.

Stress physiology offers a unique approach to the study of psychopathology because it has the potential to provide information over and above self-report measures of distress and self-regulation (Campbell & Ehlert, 2012). Adding biomarkers to psychological measures may improve diagnostic accuracy or increase predictive validity (Halford, Anderzén, & Arnetz, 2003). At the same time, individuals react very differently to stress on the level of biomarkers, and these interindividual differences can be related to a variety of developmental and psychological factors (Granger, Kivlighan, El-Sheikh, Gordis, & Stroud, 2007). Integrating models from psychology and stress physiology has a twofold potential: On the one hand, it increases our general understanding of biobehavioral response to stress; on the other, it helps to understand disorder-specific and transdiagnostic regulatory processes. This may be especially relevant for mental health conditions such as borderline personality disorder (BPD), where diagnostic heterogeneity is a common phenomenon due to 126 different ways to fulfill the minimal requirement for a valid diagnosis (American Psychiatric Association, 2013).

At the same time, BPD has been conceptually linked to stress. Several contemporary models of BPD see heightened reactivity to challenges, high levels of arousal and negative affect, and difficulties in emotional self-regulation as key features of the disorder (Linehan, 1993; Tragesser, Solhan, Schwartz-Mette, & Trull, 2007; Zanarini & Frankenburg, 2007). However, current research indicates that these factors may rather be transdiagnostic variables that are important for individuals with BPD, but do not explain the disorder sufficiently. For example, ecological momentary assessment studies reveal that neither affective instability nor switching of emotional states seem specific for BPD (Houben et al., 2016; Köhling et al., 2016; Santangelo et al., 2016). The same is true when looking at direct measures of psychophysiological arousal. Findings on reactions of the hypothalamic–pituitary–adrenal (HPA) axis and the autonomic nervous system (ANS) in individuals with BPD are mixed (Scott, Levy, & Granger, 2013; Wingenfeld, Spitzer, Rullkotter, & Lowe, 2010; Zimmerman & Choi-Kain, 2009). This indicates a need for studies that help explain these diverse findings on stress physiology in BPD. Some researchers specifically recommend investigating moderating constructs from developmental psychopathology (Wingenfeld et al., 2010; Zimmerman & Choi-Kain, 2009).

Two prominent developmental variables that have received considerable attention in BPD are early life stress and attachment. As we will explain in later sections of the article, an advantage of these variables for the study of biomarkers is that both have been linked to stress physiology. Similar to the data on psychological reactivity mentioned above, current research suggests that both childhood trauma and insecure attachment are important for understanding individuals with borderline conditions. Early research suggested a strong relationship between BPD and developmental trauma (e.g., Herman,

Perry, & van der Kolk, 1989). However, subsequent studies were not able to support this finding as particularly disorder-specific (for a discussion, see Ball & Links, 2009; Ford & Courtois, 2014; Fossati, Madeddu, & Maffei, 1999). Another research tradition conceptualized BPD as an attachment disorder (Fonagy, Gergely, Jurist, & Target, 2002; Liotti, Pasquini, & Cirrincione, 2000). Again, although attachment insecurity seems to be an important risk factor for psychopathology in general, including BPD, it is probably more a transdiagnostic than a BPD-specific construct (Levy, 2005; Levy, Johnson, Clouthier, Scala, & Temes, 2015). In other words, developmental variables such as early traumatic experiences and insecure attachment patterns are relevant for BPD, but may rather be helpful for understanding interindividual differences within the diagnosis than distinguishing it from other psychiatric disease conditions. When considering developmental variables to understand stress regulation in BPD, it is important to adopt an approach that tries to take into account their dynamic interplay. Most of the current studies utilize either main-effect models or simple diathesis-stress models on the influence of a developmental variable on human stress physiology. This suggests a linear influence of early priming on adult stress systems (Carrion & Kletter, 2012; Radley et al., 2011), or a biological model of state-related influence by a current mental disorder as biomarker or endophenotype (Goldstein & Klein, 2014; Lenzenweger, 2013). These approaches have the potential of underestimating the complexity of developmental trajectories (Haltigan, Roisman, & Fraley, 2013). For example, as specified below, different attachment styles are associated with specific self-regulatory strategies, while childhood trauma seems to be a general risk factor that influences early priming of the biological stress systems.

The aim of this study is to understand stress regulation in individuals with varying levels of BPD in the context of the impact of childhood trauma and attachment styles. Reaching beyond main-effect models, we focus on the dynamic interplay between the two variables in predicting levels of psychobiological arousal, reactivity, and recovery to a social-evaluative stressor. In the following sections, we will first describe contemporary concepts of stress regulation, then models and findings of the impact of adverse childhood experiences and attachment on stress regulation, before describing the study protocol.

INTERINDIVIDUAL DIFFERENCES: A STRESS MODEL APPROACH

A fundamental component of stress research refers to the adaptiveness of regulatory biological systems. Expanding on ideas from classical concepts of homeostasis regulation, one of the most influential contributions to the understanding of stress and disease stems from the model of allostasis and allostatic load (Karatsoreos & McEwen, 2011; McEwen & Wingfield, 2010). *Allostasis* refers to adaptive processes of body and brain to changing internal or external demands by providing optimal levels of anticipation and energy mobilization. In addition, the effective down-regulation of arousal systems

in the absence of demands is considered central for biological functioning. Chronic or repeated stress results in high, sometimes deleterious demand on the organism to adapt, called *allostatic load* (Koolhaas et al., 2011). While general mechanisms from the allostatic load model have stimulated a large body of research, empirical results regarding psychophysiology depend on a variety of known and yet to be explored predictor variables (Kudielka, Hellhammer, & Wust, 2009). In addition, while the model focuses on mechanisms of adaptation and disease development, it underemphasizes possible developmental trajectories of stress response (Juster et al., 2011). Some of these issues are addressed by current approaches, such as the adaptive calibration model (Del Giudice, Ellis, & Shirtcliff, 2011; Del Giudice, Hinnant, Ellis, & El-Sheikh, 2012; Essex et al., 2011). Key features of the adaptive calibration model are the focus on the integration of allostasis, life history, and the functioning of long-term, regulatory feedback loops. Furthermore, this model describes different physiological "phenotype" patterns in the context of their developmental history and biological responses. The model seems especially relevant for the study of developmental variables in BPD because it adds to previous ideas on stress regulation the perspective of interindividual differences related to adverse childhood experiences in a testable form. In the following section, we will summarize specific findings regarding the impact of childhood trauma on psychobiological arousal.

THE IMPACT OF ADVERSE CHILDHOOD EXPERIENCES ON BIOBEHAVIORAL REGULATORY FUNCTION

The detrimental impact of adverse childhood experiences and trauma on adult health places a major burden on individuals and society (Edwards, Holden, Felitti, & Anda, 2003; Felitti et al., 1998). A significant part of this strain is attributed to altered stress sensitivity by early life stress, influencing susceptibility to later life stressors (Harkness, Bruce, & Lumley, 2006), as well as to alterations of psychophysiological pathways (Ehlert, 2013). The general hypothesis of alterations of psychophysiological pathways by a negative impact of early life stress as well as adult trauma has been tested in a growing number of studies over the past 20 years (Ehlert, 2013; Heim & Nemeroff, 2001). Results on the impact of adult traumatic experiences on HPA-axis function are diverse. Although differences in HPA functioning have been described in studies using healthy control groups (Zoladz & Diamond, 2013), evidence suggests that it is not just state symptoms of posttraumatic stress disorder (PTSD) that drive changes in HPA reaction. For example, a meta-analysis by Klaassens, Giltay, Cuijpers, van Veen, and Zitman (2012) found no difference in overall cortisol levels between individuals exposed to a traumatic event versus those without such exposure. The results of another meta-analysis, incorporating studies of childhood trauma in addition to adult exposure to adverse experiences, show higher cortisol output in close temporal proximity to the adverse situation, but lower levels of cortisol secretion when more time has elapsed since the traumatic event (Morris, Compas, & Garber, 2012). The influence of adverse childhood experiences, but not current PTSD diagnosis, on cortisol levels is

also supported by a study by van Voorhees, Dennis, Calhoun, and Beckham (2014). Similarly, recent traumatic events were related to hypercortisolism, but more time elapsed since the event was associated with relatively lower levels of cortisol in children (de Bellis & Zisk, 2014; Carrion & Kletter, 2012). In a mixed sample, Carvalho Fernando et al. (2012) found specific adverse childhood experiences to be more predictive of salivary cortisol levels and reaction after dexamethasone suppression test (DST) than other variables, including depression or BPD symptoms, indicating a transdiagnostic psychopathological process. However, a large study by Holleman, Vreeburg, Dekker, and Penninx (2012) saw no clear main effect of childhood trauma on cortisol level or reaction after adjusting for covariates. Taken together, the majority of the available studies suggest that adverse childhood experiences may affect adult HPA stress reactions in at-risk samples, and that developmental timing, time elapsed since trauma, and measurement issues are important variables to consider when trying to generalize the results. Nonetheless, contradictory findings indicate that the exact influence of childhood trauma on stress sensitivity in adulthood remains insufficiently understood.

Despite its solid empirical base, research on associations between childhood trauma and adult stress reaction places less emphasis on how social-cognitive mechanisms influence psychophysiological reactions. For example, stress responses are associated with psychopathological states (Ehrenthal, Herrmann-Lingen, Fey, & Schauenburg, 2010; Llera & Newman, 2014), which in turn are prone to be influenced by mechanisms of worry and rumination (Ottaviani, Shapiro, & Couyoumdjian, 2013). Because a substantial proportion of social-cognitive mechanisms influence stress reaction outside of conscious processes (Brosschot, 2010) or through challenges to the self-concept (Papousek, Paechter, & Lackner, 2011), there is a need for models that help to predict which psychological processes individuals use for self-regulation. A cogent developmental model of interindividual differences in psychological regulatory capacity is described by attachment theory.

ATTACHMENT AND PSYCHOLOGICAL REGULATORY FUNCTION

The attachment motivational system emerges in early childhood, depending on contingency and coregulatory quality of interactions with the primary caregivers (Bretherton & Munholland, 2008). The main goals of attachment system activation in childhood are the (re-)establishment of proximity with an attachment figure, contact maintenance, and a state of felt security. So-called internal working models of attachment are social-cognitive representational structures that serve to integrate and interpret relational information and regulate attachment-oriented motivation, cognitions, emotions, and behavior (Dykas & Cassidy, 2011). In children and adults, there are three organized attachment styles: secure, avoidant, and anxious. Prototypically secure individuals enjoy close relationships and are able to adequately regulate proximity to significant others. Prototypically avoidant persons are usually uncomfortable relying on others in times of distress, deny

interpersonal needs, and deactivate attachment-related cognitions. Anxious individuals see themselves as insufficient with respect to self-regulatory competence and have a tendency for a hyperactivation of the attachment system. Their attempts to secure the attention and proximity of others are often accompanied by emotional hyperarousal and clinging or controlling behavior. In addition to the three organized styles, a fourth category is related to unresolved attachment trauma and loss (e.g., Bernier & Meins, 2008; Madigan et al., 2006). Individuals with this kind of attachment classification experience seemingly contradictory relationship needs, wishes, and behaviors, resulting from the impact of incoherent, fragmented representational structures of the self and others, in parallel to relationship patterns observed in patients with BPD (Levy, 2005). A central theoretical aspect of internal working models is the conceptualization of organized insecure attachment strategies as defensive regulatory processes, which are "mental mechanisms aimed at adaptation and self-regulation" (Mikulincer, Shaver, Cassidy, & Berant, 2009, p. 294). Attachment-related regulatory strategies are usually activated to regulate distress resulting from rejection, loneliness, fear, and further consequences of unaccomplished relational needs. Based on these strategies, contemporary models of attachment (Mikulincer, Shaver, & Pereg, 2003) allow the prediction of dynamic aspects of attachment security and insecurity (e.g., Coan, 2010; Ein-Dor, Mikulincer, & Shaver, 2011; Rusk & Rothbaum, 2010; Sadikaj, Moskowitz, & Zuroff, 2011). In addition, attachment-related excitatory and inhibitory feedback loops can be used to understand how co- and self-regulatory processes lead to stability or change of attachment representations (Diamond, 2001; Sbarra & Hazan, 2008). Attachment-related regulatory function depends on an individual's predominant attachment style. Anxious attachment is associated with the above-mentioned hyperactivation and hypersensitivity to attachment related cues and a negative view of the self. Attachment avoidance and its related down-regulation of relational cognitions and emotions, on the other hand, seems to be associated with a more positive view of the self (e.g., Ehrenthal, Dinger, Lamla, Funken, & Schauenburg, 2009). However, avoidant regulatory functioning is more fragile and prone to failure. Initially adaptive avoidant strategies may break down under conditions of emotional or cognitive load (Gillath, Giesbrecht, & Shaver, 2009). Also, while individuals with attachment anxiety are challenged by relational threats such as separation, avoidant individuals react more strongly to evaluative, self-challenging situations, such as real or imagined failure in an achievement task (Mikulincer, 1998). It remains an open question if the model by Mikulincer et al. (2003) may be limited for research in personality disorders because it was tested mostly in relatively healthy student samples and does not incorporate assumptions on the level of integration and coherence of the attachment system. This could be relevant for the study of BPD because individuals with a very low level of integration and coherence of internal working models, related to high levels of unresolved relational childhood trauma, may react differently to stressors than individuals with higher levels of integration of the attachment system.

THE IMPACT OF ATTACHMENT STRATEGIES ON BIOBEHAVIORAL REGULATORY FUNCTION

Although attachment insecurity is a normal facet of development, theoretical as well as empirical evidence suggests that insecure attachment may narrow regulatory strategies and therefore serve as a risk factor for health-related outcome. Known pathways include impaired biological stress physiology as well as reduced abilities for an adequate social modulation of stress (Maunder & Hunter, 2001, 2008). Although stress regulation is a central function of attachment theory (Gunnar, Brodersen, Nachmias, Buss, & Rigatuso, 1996), systematic psychophysiological research in this area started to unfold just over the past two decades (Diamond, 2001). Central to all cited approaches is the emphasis on attachment-related interindividual differences, the importance of interpersonal coregulation, and the intertwinement of psychological factors and psychophysiology, such as reaction of the HPA axis (Dykas & Cassidy, 2011; Sbarra & Hazan, 2008).

Research on HPA functioning and adult attachment differs widely with regard to methods used and results (Diamond & Fagundes, 2010). Existing studies can be grouped according to their way of assessing attachment (e.g., by questionnaire or interview). A number of articles on attachment and HPA function have been published that make use of self-report measures of attachment styles. A large study by Kidd, Hamer, and Steptoe (2011) found a blunted cortisol response to two nonsocial, behavioral tasks for individuals classified as "fearful" (individuals reporting high levels of both attachment/separation anxiety as well as attachment avoidance). In a reanalysis of cortisol patterns from the Whitehall II cohort, preoccupied attachment was related to higher levels of cortisol as well as less decrease of cortisol output over the day (Kidd, Hamer, & Steptoe, 2013). Quirin, Pruessner, and Kuhl (2008) reported a higher cortisol response to an acute stressor, but a lower cortisol awakening response to be associated with higher attachment anxiety in healthy women. Gordon et al. (2008) found attachment anxiety to be related to cortisol in a sample of young adults. Cortisol reaction during a group-related stress paradigm was greater in women with higher attachment anxiety scores (Smyth et al., 2015). In a small study with healthy women by Tops, van Peer, Korf, Wijers, and Tucker (2007), the attachment subscale of the Temperament and Character Inventory, which may serve as a proxy for tendencies to communicate and relate to friends with regard to one's own emotional states and needs, was negatively related to higher plasma cortisol levels. Smeets (2010), however, found no associations between attachment and cortisol reaction in a sample of 68 healthy participants. Fewer studies have related interview-based attachment classifications to cortisol reaction. Scheidt et al. (2000) found an association between a more pronounced cortisol response during the administration of an Adult Attachment Interview (AAI) and higher levels of dismissing attachment in patients with idiopathic spasmodic torticollis, but not for healthy control participants. Rifkin-Graboi (2008) reported no evidence for a correlation between attachment insecurity and ambulatory cortisol responses, but there was an association between the AAI dismissing

idealization subscale and higher cortisol levels after an attachment-activating memory task. And finally, Pierrehumbert et al. (2009) compared women who had and had not experienced sexual abuse in childhood or adolescence, and simultaneously applied the AAI to measure the individuals' attachment states of mind. Pierrehumbert et al. found the most suppressed cortisol reaction to a standardized laboratory stress induction task in a subgroup of women with a combination of abuse experience as well as a classification as unresolved with regard to attachment trauma in the AAI.

To sum up, research using attachment questionnaires found some evidence for an impact of attachment insecurity on cortisol reaction. However, although more studies report a specific impact of attachment anxiety, there are data favoring attachment avoidance as well. In addition, there is evidence that with a lower level of general integration of internal working models of attachment, which is often seen in individuals with repeated traumatic childhood experiences, cortisol reaction may be suppressed.

THE CURRENT STUDY

Although research on the impact of adverse childhood experiences and trauma on BPD and adult stress physiology has advanced over the past decades, conflicting findings call for further research on individual differences in biobehavioral regulatory function. Recent models of stress regulation propose a nonlinear, moderated impact of childhood trauma on the HPA axis. At the same time, developmental models of social cognition, such as attachment theory, provide a framework to understand the moderating impact of hyperactivation and down-regulation in the face of threat. Therefore, our study aims at testing the moderating influence of adult attachment strategies on the impact of adverse childhood experiences on psychophysiological stress regulation. In other words, we hypothesized that interactions between childhood trauma and attachment insecurity would significantly predict psychophysiological stress reaction in individuals with varying levels of BPD symptoms.

METHODS

PARTICIPANTS

Participants were recruited in the greater State College area, either from an outpatient community mental health clinic or from a pool of university students and community residents following screening procedures described by Scott et al. (2013). Individuals diagnosed with psychotic disorders, Bipolar I disorder, delirium, dementia, mental retardation, heart disease, endocrinological diseases (with the exception of diabetes and thyroid disorders; Jones et al., 2004), pregnancy during the preceding 6 months, or current lactation were excluded.

Participants' characteristics are displayed in Table 1. The sample consisted of 113 women who were on average in their mid-20s, ranging in age from 18 to 48 years, and predominantly White/Caucasian, with about 10% identifying as African American. A little over 40% had achieved a high

TABLE 1. *Participants' Characteristics*

Variables	*M* (*SD*) or %
Age	25.86 (8.33)
Race White/Caucasian	77.9
Highest level of education	
High school graduate or GED	42.5
> High school graduate	57.5
Currently employed (full or part time)	40.7
Relationship status	
Single	75.2
Number of medications	1.21 (1.96)
Number of BPD criteria	2.10 (2.74)
Number of non-BPD Axis II diagnoses	.15 (.36)
Number of Axis I diagnoses	.46 (.87)
NEO Angry hostility	56.97 (13.42)
NEO Anxiety	55.01 (12.13)
NEO Depression	55.29 (15.18)
NEO Impulsiveness	51.96 (12.66)
CTQ Total score	42.42 (19.58)
ECR-R Attachment anxiety	3.18 (1.37)
ECR-R Attachment avoidance	3.06 (1.22)

Note. GED = General Educational Development Test; BPD = borderline personality disorder; NEO = Revised NEO Personality Inventory; CTQ = Childhood Trauma Questionnaire; ECR-R = Experiences in Close Relationships–Revised Questionnaire.

school degree; the majority of the other participants (41.6% of the total sample) had finished partial 4-year or standard college. Eight participants had completed a master's-level degree, and two had a doctoral-level degree. Only 17.7% worked full time. Thirty-four participants had a diagnosis of BPD, and five a subthreshold BPD but exhibited prominent symptoms that would justify a BPD diagnosis. The number of additional, non-BPD *DSM-IV* Axis II diagnoses ranged from zero to two, the number of current Axis I diagnoses from zero to six. On average, participants took about one medication at the time of the study, ranging from zero to ten (more data on medication are available on request).

PSYCHOSOCIAL STRESSOR

Stress induction was performed with a social-evaLuative stress protocol, the Trier Social Stress test (TSST; Kirschbaum, Pirke, & Hellhammer, 2004). It comprises two stressful tasks (public speaking, mental arithmetic) in front of a stern and evaluative jury of confederate "judges." The tasks are preceded by a standardized baseline resting phase and followed by a recovery phase. The TSST is known to reliably elicit HPA reaction (Foley & Kirschbaum, 2010).

MEASURES

Adverse Childhood Experiences. To assess adverse childhood experiences, we administered the Childhood Trauma Questionnaire (CTQ). The CTQ measures self-reported physical, sexual, and emotional abuse, as well as physical and emotional neglect, on 28 items (Bernstein & Fink, 1998; Scher, Stein, Asmundson, McCreary, & Forde, 2001). We used the total sum score of the abuse and neglect scales as a measure of general adverse childhood experiences.

Attachment. Attachment styles were measured with the Experiences in Close Relationships–Revised questionnaire (ECR-R). It assesses attachment-related anxiety and avoidance on 36 items addressing romantic relationship expectations and experiences (Fraley, Waller, & Brennan, 2000) and has shown good psychometric properties (Fairchild, 2006; Sibley, Fischer, & Liu, 2005).

Trait Negative Affect. To control for possible impacts of trait negative affect and impulsivity, the facet scales Angry Hostility, Impulsivity, Depression, and Anxiety from the Revised NEO Personality Inventory (Costa & McCrae, 1992) were administered to all participants.

Diagnostic Status. Psychological diagnoses were assessed using the Structured Clinical Interview for *DSM-IV* (SCID-I-CV; First, Spitzer, Gibbon, & Williams, 1997) and the International Personality Disorder Examination (IPDE; Loranger, 1999) to generate reliable diagnoses of *DSM-IV* personality disorders. Both interviews were administered by experienced, trained raters at graduate student level who were blind to the initial recruitment background.

Other Covariates. Other questions aimed to assess additional possible covariates, such as food and beverage intake, sociodemographic data, body mass index (BMI), dental hygiene, sleep patterns, physical activity, and menstrual cycle, as well as overall substance use or recent life stress.

PROCEDURE

At the first appointment, all participants provided written informed consent, thereafter completing the diagnostic interviews and questionnaires. On a second appointment, participants returned for the TSST. They were instructed to neither drink alcohol 24 hours before the TSST nor use any nonprescribed medication or drugs 6 hours before examination. In addition, they were asked to restrain from caffeine or tobacco consumption as well as dental work for 4 hours prior to the test. A standard regime regarding consumption of foods and other beverages, dairy, citrus fruits, and sleep was administered. All participants were scheduled during the follicular phase of their menstrual cycle. The measurements took place during the afternoon for each individual participant in order to control for daily fluctuation of cortisol output. Before each testing session, these prerequisites were monitored; if participants had not been able to comply, their session was rescheduled.

After arriving at the lab, participants rinsed their mouth with water, completed some basic questionnaires, provided the first saliva sample, then sat quietly for the baseline period. Eight saliva samples per person were collected during the assessment by the passive drool method: –40 minutes, –30 minutes, directly before the TSST, directly after the TSST, +10 minutes, +20 minutes, +30 minutes, and +40 minutes. From the samples, cortisol as a measure of HPA reaction and alpha-amylase as a marker of ANS function were derived (Granger, Hibel, Fortunato, & Kapelewski, 2009; Kudielka, Gierens, Hellhammer, Wust, & Schlotz, 2012; Nater & Rohleder, 2009).

SALIVA COLLECTION, CORTISOL, AND SALIVARY ALPHA-AMYLASE ASSAY

Saliva samples were assayed for cortisol in duplicate using a commercially available enzyme immunoassay (Salimetrics, LLC, Carlsbad, CA). The assay uses 25 microliters of saliva per determination, has a lower limit of detection of 0.003 µg/dL, standard curve range from 0.012 to 3.0 µg/dL, and average intra- and interassay coefficients of variation less than 5% and 10%, respectively. Samples were assayed for alpha-amylase using a commercially available kinetic reaction assay (Salimetrics, LLC), which employs a chromagenic substrate, 2-chloro-*p*-nitrophenol, linked to maltotriose. The enzymatic action of alpha-amylase on this substrate yields 2-chloro-*p*-nitrophenol, which can be measured spectrophotometrically at 405 nm using a standard laboratory plate reader. The amount of alpha-amylase activity present in the sample is directly proportional to the increase (over a 2-min period) in absorbance at 405 nm. The intra-assay variation (CV) based on 30 replicate tests was less than 7.5%. The interassay variation based on 16 separate runs was less than 6%.

DATA PREPARATION

Cortisol and salivary alpha-amylase (sAA) data were inspected for distribution and outliers. Outliers, defined as ±3 *SD* away from the group mean, were winzorized (Tukey, 1977), relating to 5.7% of the cortisol as well as the sAA data. Prior to all analyses, due to their skewness, sAA values were square-root-transformed, and cortisol values were log-transformed.

STATISTICAL ANALYSES

To assess cortisol and sAA during resting, reactivity, and recovery, we implemented a coding procedure described by Llabre, Spitzer, Saab, and Schneiderman (2001). Eight units of time were constructed by dividing the minutes passed since first measurement by 10. Slower bioreactivity of cortisol compared to sAA was accounted for by implementing different coding schemes, as described in more detail elsewhere (Scott et al., 2013).

For each biomarker, we applied three mixed-models analyses to separately assess effects of psychological predictors for resting phase, reactivity, or recovery, while simultaneously controlling for the impact of the other two phases. Time (resting phase, reactivity, recovery) served as a Level 1 (i.e.,

within-person) predictor, and CTQ and ECR-R as Level 2 (i.e., between-person) predictors (Garson, 2013). Intercept and slopes for each time phase were treated as random effects with an unstructured covariance matrix. We examined both main and interaction effects of the CTQ and ECR-R anxiety and avoidance subscales for predicting intercepts and slopes (i.e., change) during each phase. Covariates such as age, medication, day in menstrual cycle, time of day, or NEO-PI-R subscales were included if they were at least marginally significant ($p < .10$) and contributed to better fit indices of the particular model. We also checked whether the expected associations between childhood trauma, attachment, and biomarkers were not just artifacts of BPD diagnosis by adding the number of BPD symptoms, and their interaction with time, to the analyses. All analyses were conducted with IBM SPSS 22 (IBM Corp., Armonk, NY).

RESULTS

All baseline models indicated a significant amount of variance to be explained at the participants' level (Hox, 2002). For cortisol, time was a significant Level 1 predictor, indicating a relative change in cortisol from the beginning of each phase to the end of each phase. Specifically, there was a decline in cortisol levels during rest, followed by an increase in cortisol during reactivity to the TSST, and a decrease during recovery after the TSST (see Table 2). Time was a significant Level 1 predictor for sAA levels during reactivity to and a significant negative predictor for recovery from the TSST, with the expected pattern of an increase during and a decrease after the stressor (see Table 3).

TABLE 2. *Cortisol Reaction to the TSST*

	Resting		Reactivity		Recovery	
	Coeff.	*t*	Coeff.	*t*	Coeff.	*t*
Level 1						
Time	−.032	−3.351**	.210	7.422***	−.075	−5.672***
Level 2						
CTQ	.004	1.213	.004	1.318	.004	1.243
ECR-R Anxiety	.023	.468	.041	.876	.034	.734
ECR-R Avoidance	.006	.126	.003	.055	.001	.025
CTQ × ECR-R Anxiety	−.0002	−.097	−.001	−.380	−.002	−.556
CTQ × ECR-R Avoidance	−.001	−.470	−.0001	−.042	< .0001	−.005
Time × CTQ	−.0002	−.397	−.001	−1.322	−.001	−1.328
Time × ECR-R Anxiety	.004	.499	−.030	−1.565	−.008	−.911
Time × ECR-R Avoidance	−.003	−.347	−.006	−.301	−.001	−.139
Time × CTQ × ECR-R Anxiety	−.001	−1.625	−.002	−2.031*	−.001	−1.444
Time × CTQ × ECR-R Avoidance	.001	1.484	.0005	.450	.0001	.365

Note: TSST = Trier Social Stress Test; CTQ = Childhood Trauma Questionnaire; ECR-R = Experiences in Close Relationships–Revised Questionnaire. All models controlled for the respective other two time-variables (i.e., resting, reactivity, recovery) and specific covariates that contributed significantly ($p < .10$) to the model as specified in the Methods and Results sections. ‘$p < .10$. *$p < .05$. **$p < .01$. ***$p < .001$.

TABLE 3. *Alpha-Amylase Reaction to the TSST*

	Resting		Reactivity		Recovery	
	Coeff.	*t*	Coeff.	*t*	Coeff.	*t*
Level 1						
Time	−.115	−1.328	.963	7.893***	−.788	−10.134***
Level 2						
CTQ	.015	.708	.0001	.006	−.0001	−.008
ECR-R Anxiety	.016	.527	.243	.859	.164	.550
ECR-R Avoidance	.679	2.339*	.692	2.622*	.676	2.174*
CTQ × ECR-R Anxiety	.021	1.615	.025	2.081*	.028	2.168*
CTQ × ECR-R Avoidance	.041	2.686**	.044	3.149**	.043	2.825**
Time × CTQ	−.007	−1.548	−.002	−.405	−.001	−.260
Time × ECR-R Anxiety	−.001	−.019	−.050	−.817	−.002	−.047
Time × ECR-R Avoidance	−.002	−.029	−.0011	−.174	.016	.369
Time × CTQ × ECR-R Anxiety	−.001	−1.548	−.008	−2.795**	−.005	−2.526*
Time × CTQ × ECR-R Avoidance	−.004	−1.503	.004	1.148	.002	1.055

Note. TSST = Trier Social Stress Test; CTQ = Childhood Trauma Questionnaire; ECR-R = Experiences in Close Relationships–Revised Questionnaire. All models controlled for the respective other two time-variables (i.e., resting, reactivity, recovery) and specific covariates that contributed significantly ($p < .10$) to the model as specified in the Methods and Results sections. *$p < .05$. **$p < .01$. ***$p < .001$.

CHILDHOOD TRAUMA

There were no significant associations between levels of childhood trauma and cortisol or sAA during resting state, reactivity, or recovery.

ATTACHMENT

There was no main effect of attachment anxiety on cortisol or sAA during resting state, reactivity, or recovery. ECR-R attachment avoidance was significantly associated with higher levels of sAA in all three phases.

INTERACTION OF CHILDHOOD TRAUMA AND ATTACHMENT

Cortisol reaction to the TSST interacted significantly with CTQ and ECR-R anxiety: For individuals with higher levels of adverse childhood experiences, higher attachment anxiety was associated with a less steep increase in cortisol during the reactivity phase.

Regarding sAA, there was a significant positive interaction effect between CTQ and attachment avoidance during all three phases, and a significant positive interaction effect between CTQ and ECR-R anxiety on sAA during reactivity and recovery. We also found a three-way interaction among time, CTQ, and attachment anxiety, in that for individuals with higher CTQ values, more attachment anxiety was associated with less reactivity, and more recovery of sAA (see Table 3).

COVARIATES AND IMPACT OF BPD SYMPTOMS

Regarding cortisol, for all three phases, the time the participant had been awake that day was the only significant covariate. Running the models with a full set of all possible covariates did not change the results. The number of IPDE BPD criteria did not show any significant associations with cortisol levels or time-related change in cortisol output. Furthermore, both changes of the modeling approach did not alter any of the other results. For sAA, significant covariates were the NEO anxiety and depression subscale and the number of days in menstrual cycle. Running the models with a full set of all possible covariates did not alter the results. Entering number of IPDE BPD criteria or BPD-criteria by time interactions into the model did not change the results or display any significant associations with the biomarkers.

DISCUSSION

In a study on 113 women with varying levels of BPD pathology, there was an impact of psychosocial variables on HPA as well as sympathetic nervous system (SNS) reaction to a social-evaluative stressor. Especially attachment avoidance was especially related to generally elevated levels of sAA. Interactions between higher levels of childhood trauma and attachment insecurity (avoidance and, to a lesser degree, anxiety) were associated with higher levels of SNS activation as well. Under conditions of higher levels of childhood trauma and adversity, attachment anxiety was related to dampened HPA reactivity, reduced SNS reactivity, and more SNS recovery.

An important finding of our study is that variables from the tradition of developmental psychopathology were more helpful than BPD symptoms for predicting HPA and SNS activity in a sample of women with varying levels of personality functioning. In other words, adding the number of BPD symptoms or their interaction with time to the statistical model neither added to nor changed the pattern of results. Instead, attachment avoidance and the interaction between adverse childhood experiences and attachment insecurity were related to higher levels of ANS functioning, especially regarding the SNS.

From the perspective of attachment theory, this can be understood as a breakdown of attachment regulatory functioning, under either conditions of the social-evaluative stressor or the moderating influence of an internal risk factor, childhood trauma. Although attachment avoidance may be helpful in the down-regulation of stressful memory content (Dykas & Cassidy, 2011), this effect disappears under conditions of stress and psychological load (Gillath et al., 2009). Similarly, the evaluative aspect of the TSST could be especially stressful for individuals with high levels of avoidance (Mikulincer, 1998). This could also explain the larger influence on sAA, which is more prone to react rapidly to, and be prolonged through, psychological processes such as rumination and perseverative cognitions (e.g., Ottaviani et al., 2013). More overall activation of the SNS could lead to a psychobiological restriction of reactivity of the ANS, as well as to a general blunting of the stress response due to prolonged allostatic load (Juster, McEwen, & Lupien, 2010). Especially

the developmental combination of attachment hyperactivation and the risk factor childhood trauma would lead to a constant hyperactivation of the stress systems over the life span. The lower levels of HPA reactivity could then be a consequence of counterregulatory mechanisms, a preventive dampening of stress response, also described by Scott et al. (2013) for individuals with BPD, or Kidd et al. (2013) for preoccupied attachment. Interestingly, this would fit into the "vigilant pattern" of the adaptive calibration model described by Del Giudice and colleagues (2011), which is assumed to develop in unpredictable or dangerous childhood conditions. At the same time, heightened levels of cortisol or sAA may in turn negatively influence encoding and processing of emotional and trauma-related stimuli, resulting in a deleterious regulatory feedback loop (Holz, Lass-Hennemann, Streb, Pfaltz, & Michael, 2014; Nicholson, Bryant, & Felmingham, 2014).

Our results do not support previous findings on a possible main effect of attachment anxiety on cortisol reaction. On the one hand, this could be due to sample effects. In contrast to other studies, we included women with low levels of personality dysfunction as well as women fulfilling full criteria for *DSM-IV* BPD diagnoses. By broadening the range of psychopathology, we also intended to broaden the variability of attachment and CTQ ratings. Studies with exclusively nonclinical or clinical samples are at a risk of over- or underestimating true effects of attachment and childhood trauma on stress reaction, especially when taking into account that individuals can have different ranges of psychobiological responsiveness (Del Giudice et al., 2011). For example, according to the perspective of allostatic load, for individuals in the upper range of attachment security, attachment anxiety could stimulate a larger cortisol reaction because the organism can rely on adaptive downregulation on a psychological as well as a biological level.

Strengths of the study are a reasonably large, well-diagnosed sample of women with varying degrees of BPD symptoms, attachment insecurity, and childhood trauma. This is important not only for ensuring enough variance to be explained in the models, but also for addressing these questions from a perspective that explicitly tries to capture dimensions not only of psychopathology, but also of normal behavior and regulatory processes (Cuthbert & Kozak, 2013). We also made an effort to control for covariates that possibly influence cortisol or sAA measurements. And lastly, by using a mixed-model approach, we were able to test the influence of our psychological predictors while simultaneously controlling for the influence of possibly competing variables. This is relevant because early life stress and attachment insecurity share some conceptual overlap, namely the influence of actual experiences in an interpersonal context. At the same time, attachment formation needs the activation of the attachment system and focuses on repeated micro-interactions (Beebe et al., 2010), whereas the occurrence of adverse childhood experiences is not bound to attachment-related situations, and single events such as accidents are possible. In that regard, studying the impact of both variables simultaneously could help to disentangle their specific influences, especially when using a cross-sectional design. In our study, the risk factor of childhood trauma had less impact than the psychological variable of attachment for HPA and ANS reaction.

Possibly relevant limitations of the study are the exclusive focus on women and the use of questionnaire data for assessing attachment. Excluding men may help to reduce gender-related variance (Bangasser & Valentino, 2012), but it affects the generalizability of our results. Applying questionnaire assessment of attachment instead of interview-based data could also limit the understanding of the effects by not being able to directly assess different levels of personality functioning of attachment (Blatt & Levy, 2003; Roisman et al., 2007). In other words, individuals with disorganized internal working models of attachment may not be able to rely on stable strategies to regulate themselves in comparison to individuals with organized attachment styles. Future studies, especially in the context of BPD, should apply both self-report and interview measures of attachment. Furthermore, while our predictor variables come from a tradition of developmental psychopathology, they measure current state of mind with regard to attachment, and current representations of childhood trauma. It would be interesting to address these questions in a sample from a longitudinal study with actual data from early childhood and adolescence. And last, but not least, we simultaneously tested the impact of our predictors on psychobiological functioning, controlling for effects of all the other variables, which may reduce the variance explained by each predictor if entered separately.

Our results allow for some tentative comments on possible implications for the study of BPD and its treatments. First, as mentioned above, it may be helpful to complement classical BPD diagnosis according to the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) by other approaches, at least when looking at biological markers. The NIMH Research Domain Criteria (RDoC; Insel et al., 2010) initiative of studying proposed subsystems of psychobiological behavior is obviously one way of organizing research in the hope of reducing or explaining diagnostic heterogeneity. RDoC proposes a set of fundamental, transdiagnostic constructs hypothesized to be at the basis of human behavior and psychopathology, namely negative and positive valence systems, systems related to cognitive and social processes, and arousal and regulatory systems. While the inconsistencies regarding BPD described in the introduction can be seen as a prime example for the necessity of the RDoC approach, it seems important to exercise caution and not draw premature conclusions (Lilienfeld, 2014). Despite the attempt to extract empirically driven dimensions of personality and psychopathology, its current empirical basis is heavily influenced by major research traditions from biological psychiatry, but also other areas of psychopathology. In fact, our results indicate that at this moment, a viable approach to making sense of RDoC for psychopathology and psychotherapy is to combine it with strong theoretical models from psychology. In the RDoC terminology, we used the "attachment" construct from the domain "social processes" together with the developmental risk factor "adverse childhood experiences" to understand interindividual psychophysiological differences in the construct "arousal" of the domain "arousal and regulatory systems." This theory-driven approach is of special relevance for psychosocial treatments of BPD because in the RDoC approach there is a tendency to favor possible biological substrates (Cuthbert & Kozak, 2013) over well-known psychological theories, but also over therapy-oriented diagnostic

models (e.g., Oldham, 2015; Skodol et al., 2011). For future studies, it might be helpful to integrate these and other approaches (Zimmermann et al., 2012) wherever possible, rather than to repeat old research programs under a new nomenclature.

At the same time, adding RDoC-oriented measures to existing paradigms from psychopathology can help to clarify disease mechanisms and mechanisms of change as targets for psychotherapy interventions. For example, transference focused psychotherapy (TFP) has been shown to increase attachment security and reflective functioning (Fischer-Kern et al., 2015; Levy et al., 2006). Although other approaches to the treatment of BPD, for example, dialectical behavior therapy (DBT), are generally open to understanding interpersonal patterns and processes, for example, regarding changes in patient introjects (Bedics, Atkins, Comtois, & Linehan, 2012), they still failed to show changes in attachment representations. The increase in coherence of the narratives on early attachment experiences in TFP may be directly related to more integrated representations of the self and others, which is central to the treatment model. A next step could be to delineate to what extent the increase in attachment security is related to short- or long-term increases in psychosocial functioning. Integrating this idea into the context of our study, it would be possible to test if an increase in attachment security is related to better psychophysiological recovery from a stressor after experimental activation of the representation of an attachment figure (Bryant & Chan, 2015). Similarly, multiple measurement points of attachment representations, but also attachment-related over the course of interventions are needed to delineate if increase in attachment security precedes symptom change in TFP or other treatments, or vice versa (e.g., Daniel, Poulsen, & Lunn, 2016). While both TFP and attachment theory share the view that the current representation of traumatic interactional experiences is central for the understanding of regulatory psychodynamics, and results from our study indicate the importance of childhood trauma for stress regulation, it would be interesting to see if and how TFP changes trauma-related symptoms. Here DBT has already started to combine its core program with features of other trauma-related interventions (Bohus et al., 2013; Harned, 2014). Especially in the light of promising results of nonexposure-based treatments for trauma-related disorders (e.g., Markowitz et al., 2015; Steinert et al., 2017), further research is needed to show if TFP may be a viable option for the treatment of comorbid complex PTSD in BPD as well.

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